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Note

Preparation of thioethers using S_N1-active halides and zinc mercaptides

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S_N1-Active (tertiary alkyl, allylic and benzylic) halides react with zinc mercaptides, prepared *in situ* by contacting mercaptans with either zinc carbonate or zinc sulphide, under optimised conditions, to afford thioethers in moderate to very good yields (50-95 %). The method is particularly useful for the preparation of thioethers with at least one bulky alkyl group.

Thioethers (sulphides) are an important class of organosulphur compounds that occur in odoriferous plants and foods[1]. Among several methods available for the preparation of thioethers (sulphides), the simple and general ones are, condensation of a thiol with an alkyl donor and nucleophilic substitution of an alkyl halide with an alkali metal mercaptide[2,3]. In the former method, either the mercaptan or the alkyl donor is usually activated. These methods are applicable to the synthesis of dialkyl or aryl alkyl sulphides where the alkyl groups are primary or secondary; but they do not yield satisfactory results when tertiary alkyl halides are involved, due to competitive elimination of hydrogen halide from them. Indirect methods are, therefore, used in such cases. For example, thioethers are obtained[4] from the reaction of *t*-butyl, benzyl or allyl alcohol with mercaptans in the presence of zinc iodide. Apparently, the alkyl iodides are formed here as intermediates. The reaction of zinc mercaptides, prepared *in situ*, with *t*-butyl bromide is also reported[5] to afford the corresponding sulphides in good yields. However, no other tertiary alcohol / halide has been tried in these reactions. In the present work, the reaction of zinc salt of benzyl mercaptan with tertiary halides containing bulky groups *viz*., 8-*p*-menth-1-enyl and 1-*p*-menthanyl chlorides was investigated. These substrates failed to react under the prescribed conditions[5] which prompted us to reinvestigate the reaction of zinc mercaptides with alkyl halides systematically.

t-Butyl bromide was chosen as the model substrate and its reaction with zinc salt of benzyl mercaptan, prepared by several alternative methods, was studied. Method A, involved contacting benzyl mercaptan with zinc carbonate in refluxing benzene and removing water formed by azeotropic distillation. This was followed by addition of the bromide along with a molar equivalent amount of pyridine and setting the mixture to reflux. In Method B, the solvent for the reaction was dichloromethane. In Method C, the reaction was carried out as in Method A, but in the absence of pyridine. In methods D and E, the zinc salt was prepared by contacting the mercaptan with zinc carbonate and zinc sulphide respectively in dichloromethane at ambient temperature. Then, the mixture was set to reflux with the bromide. Results of these experiments are presented in Table I.

Method A was same as the one reported earlier[5]. In fact, this is a general standardised protocol for the preparation of the zinc salts of nucleophiles used in the nucleophilic substitution of S_N1- active halides under non-solvolytic conditions[6]. Accordingly, addition of a base such as pyridine is mandatory to scavenge the zinc halide, a Lewis acid, formed in the process. Thus, efficient methods for the introduction of functional groups like hydroxyl, alkoxyl, carboxyl, azide, thio- and isothiocyanates[7] have been developed. However, difficulties are encountered with thiocarboxylates (thiolacetates)[8], as observed now with mercaptides. The substitution reaction is either extremely slow or does not take place at all in the presence of pyridine. Apparently, in these cases, the zinc

Table I—Reaction of *t*-butyl bromide with the zinc salt of benzyl mercaptan prepared by different methods under reflux conditions

Method	Solvent	Time (hr)	Yield (% isolated)
A	C_6H_6†	12	35
B	CH_2Cl_2†	24	0*
C	C_6H_6	1	89
D	CH_2Cl_2	6	93
E	CH_2Cl_2	10	95

* No reaction
† C_6H_5N

mercaptides strongly complexed with base rendering themselves unavailable for the substitution. This problem was overcome by using two molar equivalents of the salt in the reaction. Further, the zinc mercaptide appeared to be sensitive to heat, as seen by the development of red colour and decreased yield of substitution products at higher temperatures. When the zinc salt formation as well as the substitution reaction were carried out under mild conditions (methods D and E), best yields of *t*-butyl benzyl sulphide were obtained.

Further, the reactions of zinc salt of benzyl mercaptan (*ex.* methods D and E) with several representative halides were studied under the optimised conditions. The results are summarised in Table II. No product was observed in the case of primary and secondary halides (entries 1 and 2). A general feature of the zinc-salt assisted substitution of alkyl halides is their specificity to S_N1-active compounds. While methods D and E afforded excellent yields of *t*-butyl benzyl sulphide (entry 3), better yields of 1-*p*-menthanyl benzyl sulphide (entry 4) and 2-(2-phenylpropyl)benzyl sulphide (entry 5) were obtained by Method E. This may be due to the nature of the zinc salt employed (Scheme I). However, in the case of 8- *p*-menth-1-enyl, allyl and benzyl halides, Method D afforded relatively higher yields of the sulphides showing its general applicability to S_N1-active halides. The presence of double bond in the substrate, made the reaction more complex. Besides the normal substitution products, mercaptan addition products were also observed (entries 6, 7 and 8). In case of allyl bromide, considerable amounts of dibenzyl sulphide was formed, due to partial exchange of bromide group with the mercaptan.

Table II—Reaction of alkyl halides (RX) with zinc salt of $PhCH_2SH$ prepared by methods D and E

Entry no.	RX	$PhCH_2SH$			
		Method D		Method E	
		Time (hr)	Yield (%)	Time (hr)	Yield (%)
1	*n*-Propyl bromide	24	0	24	0†
2	*s*-Butyl bromide	24	0	24	0†
3	*t*-Butyl bromide	6	93	10	95
4	1-*p*-Menthanyl chloride	6	30*	10	91*
5	2-Chloro-2-phenylpropane	8	78	8	90
6	8-Chloro-*p*-menth-1-ene	4	43	4	20
7	Allyl bromide	24	50@	24	0†
8	Benzyl bromide	14	85	14	33‡

* 1:3 *cis* : *trans* mixture (GC)
† No reaction
‡ 60 % unreacted bromide recovered
@ 20% dibenzyl sulphide formed

Method D: $ZnCO_3+2\ RSH \rightarrow Zn(SR)_2+CO_2+H_2O$

Method E: $ZnS+RSH \rightleftharpoons [ZnSHSR] \overset{RSH}{\rightleftharpoons} [Zn(SR)_2+H_2S$

Scheme I—Formation of zinc mercaptides

Suitability of Method E to the preparation of thioethers from saturated tertiary alkyl halides was demonstrated by the preparation of various sulphides of *t*-butyl bromide and 1-*p*-menthanyl chloride using zinc salts of *n*-propyl. *s*-butyl, *t*-butyl, phenyl, allyl and benzyl mercaptans (Table III). The physical and spectral data of compounds are presented in Table IV.

We have described here a simple and efficient method of preparing dialkyl/alkyl aryl thioethers from the corresponding S_N1-active halides by two alternative routes. They are synthetically attractive, especially for the preparation of tertiary alkyl thioethers.

Experimental Section

GC analyses were carried on a Hewlett-Packard 5730 A gas chromatograph employing 1/8" (outer diam.) 6 ft S. S. columns having (I) 10 % OV-101 and (ii) 10% Carbowax - 20M coated on Chromosorb W (80 - 100 mesh). The ^1H NMR spectra were recorded on Varian EM-390 instrument in CCl_4 solvent using TMS as the internal standard. B.ps are uncorrected. Simple alkyl halides were either procured commercially or prepared by standard methods. 8-*p*-Menth-1-enyl, 1-*p*-menthanyl and 2-(2-phenyl)propyl chlorides were prepared by the earlier reported procedures[8].

Reaction of alkyl halide with zinc salt of a mercaptan : General procedure. A mixture of $ZnCO_3$ (2.50 g, 20 mmoles, Method D) or ZnS (1.95 g, 20 mmoles, Method E) in CH_2Cl_2 (50 mL) was stirred with a mercaptan (40 mmoles) at ambient temperature for 4hr. To the zinc salt thus obtained, alkyl halide (20 mmoles) was added and the mixture stirred under reflux until GC or TLC showed the disappearance of the halide. The reaction mixture was worked-up by successively

Table III—Reaction of zinc salts of various mercaptans (RSH) with a) *t*-butyl bromide and b) 1-*p*-menthanyl chloride.

Entry no.	RSH	*t*-Butyl-SR				1-*p*-Menthanyl-SR	
		Method D		Method E		Method E	
		Time (hr)	Yield (%)	Time (hr)	Yield (%)	Time (hr)	Yield (%)
1	n-Propyl	4	78	8	85	20	83
2	s-Butyl	3	75	10	82	12	90
3	*t*-Butyl	6	76	8	79	24	0†
4	Phenyl	4	86	8	91	14	96
5	Allyl	3	56	7	33	24	0†
6	Benzyl	6	93	10	95	10	91

* Mixtures of *cis* & *trans* isomers
† No reaction

Table IV—Physical and ^{1}H NMR data of the alkyl sulphides

Sl. No.	Compd R	(R-S-R′) R′	b.p.^{0}C/Torr	^{1}H NMR (δ)
1	*t*-Butyl	Benzyl	85 / 6	1.33 (9H, s), 3.60 (2H, s), 7.36 (5H, s).
2	1-*p*-Menthanyl	Benzyl	144 / 0.6	0.93 (6H, d, *J* = 1.8 Hz), 1.03-1.26 & 1.33-1.70 (10H, bm), 1.26 (3H, s), 3.63 (2H, s), 7.26-7.33 (5H,m).
3	2-(2-Phenylpropyl)	Benzyl	136 / 0.7	1.66 (6H, s), 3.32 (2H, s), 7.00-7.66 (10H, m).
4	α-erpinyl	Benzyl	140 / 0.7	0.83 (3H, s), 0.86 (3H, s), 1.66 (3H, s), 3.63 (2H, s), 5.38 (1H, m), 7.35 (5H, m).
5	Allyl	Benzyl	100 / 10	2.96 (2H, d, *J* = 1.8 Hz), 3.60 (2H, s), 4.90-5.23 (2H, m), 5.60-6.13 (1H, m), 7.33 (5H, m).
6	Benzyl	Benzyl	51-52 (m. p.)	3.50 (4H, s), 7.33 (10H, s).
7	*t*-Butyl	*n* Propyl	75 / 10	0.93 (3H, t), 1.33 (9H, s), 1.45 (2H, m), 2.50 (2H, t).
8	*t*-Butyl	*s*-Butyl	140 / 760	1.00 (3H, t), 1.25 (3H, d), 1.33 (9H, s), 1.45 (2H, m), 2.50 (1H, m)
9	*t*-Butyl	*t*-Butyl	153 / 760	1.35 (18H, s).
10	*t*-Butyl	Phenyl	99 / 10	1.25 (9H, s), 7.40 (5H, s).
11	*t*-Butyl	Allyl	110 / 760	1.33 (9H, s), 2.96 (2H, d, *J* = 1.8 Hz), 4.90-5.23 (2H, m), 5.60-6.13 (1H, m).
12	1-*p*-Menthanyl	*n*-Propyl	108 / 0.7	0.93 (6H, d, *J* = 1.8 Hz), 1.03-1.26 & 1.33-1.70 (15H, bm), 1.26 (3H, s), 2.46 & 2.33 (2H, t).
13	1-*p*-Menthanyl	*s*-Butyl	116 / 0.8	0.93 (6H, d, *J* = 1.8 Hz), 1.03-1.26 & 1.33-1.70 (18H, bm), 1.26 (3H, s), 2.50-2.60 (1H, m).
14	1-*p*-Menthanyl	Phenyl	146 / 0.7	0.93 (6H, d, *J* = 1.8 Hz), 1.03-1.26 & 1.33-1.70 (10H, bm), 1.26 (3H, s),7.26 & 7.33(5H, m).

washing with 2*N* HCl, sat. $NaHCO_3$ and water and then dried (anhydr. Na_2SO_4). The crude product obtained on removal of the solvent was either distilled or chromatographed over SiO_2 (100 - 200 mesh) using hexane-ethyl acetate mixtures as eluant to afford the corresponding pure sulphide.

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